CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-684

CORRESPONDENCE

BEDFORD LABORATORIES™

March 26, 2001

Fax Amendment/Microbiology, Labeling, and Chemistry

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

TPV

NDA UPON AMENDMENT

RE: **ANDA 75-684/ Fax Amendment**
Product: **Famotidine Injection; 10 mg/mL, 50 mL per vial Pharmacy Bulk**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial Pharmacy Bulk, in accordance with a fax deficiency received for a separate ANDA, 75-622 Famotidine Injection 10 mg/mL, 2 mL, in regards to changes to the Reference Listed Drug labeling. Form 356H is enclosed.

A. CONTAINER
Bedford Laboratories™ would like to make a Post-Approval Commitment to revise the container label to delete the statement "For the preparation... insert." and replace it with "FOR INTRAVENOUS USE ONLY AFTER DILUTION. USUAL DOSAGE: See Package Insert."

B. CARTON
Bedford Laboratories™ would like to make a Post-Approval Commitment to revise the carton to delete the statement "For the preparation... insert." and replace it with "FOR INTRAVENOUS USE ONLY AFTER DILUTION. USUAL DOSAGE: See Package Insert."

C. INSERT
The changes have been made in accordance with the Reference Listed Drug labeling approved March 14, 2001. A side-by-side comparison of the current insert revision versus the previously submitted insert is provided in Attachment II for your review. Also included in Attachment II are 12 copies of the final printed insert.

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RECD
MAR 27 2001
OGD

4/2/01

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CHEMISTRY AND MANUFACTURING CONTROLS

1.

2.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)201-3333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
MAR 26 2001
OGD

A DIVISION OF BEN VENUE LABORATORIES, INC.
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February 16, 2001

Minor Amendment

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-684/ Minor Amendment
Product: Famotidine Injection; 10 mg/mL, 50 mL per vial

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial after receiving tentative approval on January 24, 2001 as requested in the approval letter. Form 356H is provided.

The analytical method has been revised with respect to the calculation of the impurities. Previously, the method required preparation and analysis of each individual known impurity reference standard in order to quantitate any known impurities found in the samples of the drug substance. This method of calculation required significant amounts of impurity reference standards which are not readily available from the API manufacturer. Therefore, the method has been revised with the relative response factors of each of these known impurities. The RRF is used in the calculation of sample impurities instead of comparison to the actual preparation of each individual standard. Either method of calculation yields the same result and has no impact on the reporting of impurity values. A report is provided which outlines the determination of the Relative Resonse Factors of the impurities. Also included is the revised analytical method,

There have been no other changes to the Chemistry and Manufacturing Controls that were tentatively approved on January 24, 2001.

There have also been no changes to the labels or labeling that was tentatively approved. Twelve final printed copies of the label and labeling are provided.

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FEB 20 2001

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We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)201-3333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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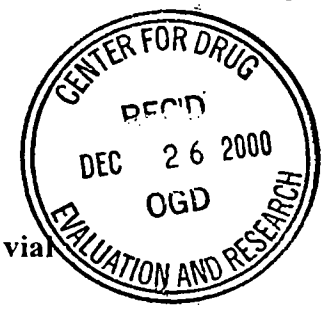
December 22, 2000

Fax Amendment/Microbiology

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT

N/A's



RE: **ANDA 75-684/ Fax Amendment**
Product: **Famotidine Injection; 10 mg/mL, 50mL per via**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial, to resolve the microbiology deficiency cited in the Agency's correspondence dated December 21, 2000.

Ben Venue Laboratories, Inc. has always maintained a "zero positives" goal for the contamination rate of a media fill. Every effort is made to reduce contamination to the lowest level possible; however, contamination rate limits have been imposed at a limit with a 95% confidence interval, based on statistical probability. Ben Venue Laboratories, Inc. is in the process of revising the relevant Standard Operating Procedure) with contamination limits based on the process capabilities and historical data, as opposed to the positives using a 95% confidence interval limit. A sampling of historical date is presented in the table below for your review:

Test No.	Date Conducted	Filling Room	Vial Size/Opening	Fill Volume	Test Status	Contamination Rate

17

Based on the aforementioned ch is

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We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440) 201-3333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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ORIG AMENDMENT

N/AM

December 1, 2000

Telephone Amendment/Chemistry

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-684/ Telephone Amendment
Product: Famotidine Injection; 10 mg/mL, 50mL per vial

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial, in accordance with a telephone discussion with Mr. Raymond Brown from the Agency and Ms. Pratima Patel and Ms. Molly Rapp from Ben Venue Laboratories. Form 356H is provided.

The Drug Substance specifications for Chromatographic Purity have been revised to include a limit for Famocyanoamidine of . Bedford Laboratories™ commits to maintaining and enforcing a mit on this impurity. The drug substance chromatographic purity method has also been revised to include the Relative Retention time of this impurity for identification and quantitation purposes. The revised specification and method are attached for your review.

In addition, the Statement of Exclusivity has been revised to reflect the Pediatric Exclusivity Period granted to the Reference Listed Drug, which will expire on April 15, 2001. The revised statement is attached.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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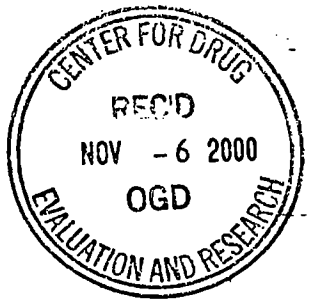
NDA ORIG AMENDMENT
N/AM

November 3, 2000

Minor Amendment
Chemistry and Microbiology Deficiencies

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855



RE: **ANDA 75-684/Minor Amendment**
Product: **Famotidine Injection; 10 mg/mL, 50 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 4 mL and 20 mL per vial. FDA Form 356h is provided in Attachment I.

A. CHEMISTRY DEFICIENCY

1.

2.

chromatogram

a

b

urity
raw

11-8-00

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Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

11/6/00

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B. MICROBIOLOGY DEFICIENCIES

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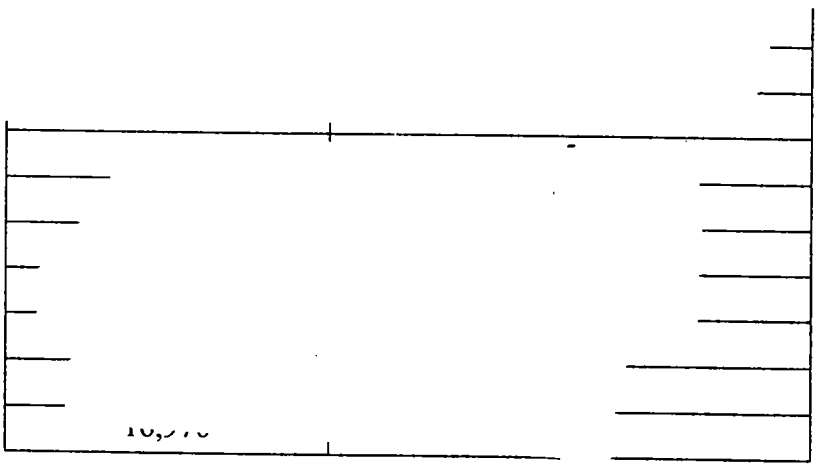
A

2. T
ii
May/June 1996 article



C. LABELING DEFICIENCIES

The container label, carton, and package insert labeling have been revised in accordance with the deficiency comments. A side by side comparison is provided in Attachment IX. Twelve copies of the final printed labeling are also included in Attachment IX.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 3333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

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June 13, 2000

Chemistry Amendment

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/Ac

RE: ANDA 75-684/Chemistry Amendment
Product: Famotidine Injection; 10 mg/mL, 50 mL per vial

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial. FDA Form 356h is provided in Attachment I. The DMF holder [redacted] was found deficient by the Agency during the review of ANDA 75-622 (Bedford Laboratories™), and has now responded to those deficiencies. A copy of the response letter is provided in Attachment II.

The impurity methods used to quantitate impurities in the drug substance and the drug product have been revised to include a sensitivity solution to be analyzed with the system suit. The sensitivity solution is prepared at a [redacted] level of the nominal concentration. This solution must generate a signal to noise ratio of ≥10 (LOQ), as a system suitablity requirement, before the samples can be analyzed, as described in the analytical test method. Method [redacted] quantitates impurities in the drug substance, and method [redacted] quantitates impurities in the drug product. Both methods are provided in Attachment III.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 14 2000
OGD

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February 28, 2000

Major Amendment / Chemistry and Labeling Deficiency

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA DRUG AMENDMENT
N/AC

RE: **ANDA 75-684/Major Amendment**
Product: **Famotidine Injection; 10 mg/mL, 50 mL per vial Pharmacy Bulk**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-684, for Famotidine Injection, 10 mg/mL, 50 mL per vial Pharmacy Bulk to remove the deficiencies cited in the Major Deficiency of February 2, 2000.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Chemistry Deficiencies:

1.

2.

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FEB 29 2000
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Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

2/28/00

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B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the evaluation of our method by the Detroit District Laboratory is still pending.

C. LABELING

1. All deficiencies cited have been corrected. Please refer to Attachment X for twelve copies of final printed vial labels, carton and package insert labeling for review. Also located in Attachment X are annotated side-by-side comparisons of the final printed package insert with the last draft package insert.

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We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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505
(j)(2)(A)
Marsam Patel

July 30, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: Abbreviated New Drug Application
PRODUCT: Famotidine Injection, 10 mg/mL, 50 mL per vial Pharmacy Bulk

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Famotidine Injection, 10 mg/mL; 50 mL vial Pharmacy Bulk. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, (Guidance for Industry, "Organization of an ANDA," OGD #1, Revised February 1999), and contains a copy of the package insert of the "listed drug" (Merck & Co., Inc, Pepcid® Injection.) and a copy of the approved citizen's petition submitted by Marsam Pharmaceuticals, Inc. Docket no. 97P-0011/CP1, Famotidine Injection Pharmacy Bulk. This application consists of three volumes.

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of our application (Famotidine Injection, 10 mg/mL; 50 mL per vial). The drug product is a solution intended solely for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Bedford Laboratories commits to provide full cooperation to resolve any problem which may arise during the methods validation testing as part of the "Post-Approval" process for the above listed drug product.

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Two copies of analytical methods which were used to test this product and an analytical method validation package are enclosed separately along with this application.

Section XXII of this application, located in Volume 3, contains the Sterilization Assurance Data and Information as well as the following: A copy of the labeling and package insert, a summary of the manufacturing process including the components and composition statement, and copies of the executed batch record containing holding times, filtration integrity testing and sterilization records.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-232-3320, ext. 333 (direct) and (440)-439-6398 (fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.